UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/463,733	06/12/2000	CHARLES ZUKER	02307E-085110US	6739

7590 12/31/2008

ANNETTE S PARENT
TOWNSEND AND TOWSEND AND CREW
TWO EMBARCADERO CENTER
8TH FLOOR
SAN FRANCISCO, CA 94111

EXAMINER	
MYERS, CARLA J	
ART UNIT	PAPER NUMBER
1634	

MAIL DATE	DELIVERY MODE
12/31/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/463,733	ZUKER, CHARLES	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-13,15,17,19,20 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-13,15,17,19,20 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 10, 2008 has been entered.

2. Applicant's arguments have been fully considered but are not persuasive to place all of the pending claims in condition for allowance.

All rejections not reiterated herein are hereby withdrawn.

Claims 1, 5-13, 15, 17, 19, 20, and 22 are pending and have been examined herein.

This action contains rejections that have been modified to address the amendments to the claims. This action is made non-final.

Claim Rejections - 35 USC § 112 – New Matter

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 5-13, 15, 17, 19, 20, and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The specification as originally filed does not appear to provide basis for the amendment to the claims to recite a method of screening for modulators of RDGC GPCR phosphatase activity wherein the method includes providing a second sample containing a mutant rhodopsin lacking the last 18 amino acids at the carboxy-terminus and a Drosophila RDGC phosphatase comprising SEQ ID NO: 1 and determining the level of RDGC GPCR phosphatase activity in the second sample, and further contacting the second sample with a test compound, and determining the level of RDGC GPCR phosphatase activity in the second sample contacted with the test compound, to thereby detect modulators of RDGC GPCR phosphatase.

The specification (page 44) as originally filed discloses a single mutant rhodopsin protein in which the COOH-terminal 18 amino acids have been deleted - i.e., Rh1Δ356. The specification (pages 43-44) teaches an assay in which "RDGC was analyzed biochemically, physiologically, and genetically to determine its activity as a GPCR phosphatase." In these assays, transgenic flies expressing the truncated rhodopsin were analyzed, as were flies expressing wildtype rhodopsin. The specification reports that "(t)he truncated receptor was expressed in near normal amounts and the cells displayed normal light response. Rhodopsin was not hyperphosphorylated in Rh1Δ356 flies."

However, the specification does not disclose the use of the truncated rhodopsin mutant Rh1Δ356 in methods of screening for modulators of RDGC phosphatase activity. There are no teachings in the specification of a method wherein steps are performed which screen for a modulator of RDGC GPCR phosphatase activity in a first sample that is contacted with a test compound, and wherein simultaneously or previously or subsequently a second sample is further provided which contains a mutant rhodopsin lacking the carboxy terminal 18 amino acids and a Drosophila GPCR phosphatase comprising SEQ ID NO: 1, and the RDGC GPCR phosphatase activity is determined in the second sample in the absence and in the presence of a RDGC phosphatase mimetic. The disclosure at page 44 of the specification of a transgenic fly comprising Rh1Δ356 does not provide basis for the distinct concept of a screening assay, performed in vitro or in cells, for modulators of RDGC GPCR phosphatase activity wherein the assay includes performing a step of providing sample comprising a mutant rhodopsin lacking the cytoplasmic terminal 18 amino acids and a Drosophila GPCR phosphatase comprising SEQ ID NO: 1 and determining the level of RDGC GPCR phosphatase activity in the sample containing the mutant rhodopsin in the presence of and absence of a RDGC phosphatase mimetic.

Additionally, the claims encompass the use of a "mutant rhodopsin comprising wild type rhodopsin lacking the last 18 amino acids at the carboyx-terminus." Since the claims do not define the “wild type” and do not define the length of the mutant rhodopsin, the claims encompass mutants in which more than 18 amino acids are deleted from the COOH-terminus. That is, mutants in which 19 or 20 or 21, etc amino

acids are deleted from the carboxy-terminus constitute mutants lacking the last 18 amino acids at the carboxy-terminus. Further, since wildtype rhodopsin (such as Rh1) does not lack the carboxy-terminal 18 amino acids, the specification does not provide support for the concept of any mutant comprising a wildtype rhodopsin lacking the carboxy-terminal 18 amino acids. The specification provides basis only for a single rhodopsin mutant – i.e., mutant Rh1Δ356, in which only the COOH-terminal 18 amino acids have been deleted. The specification does not provide support for any mutant rhodopsin in which 18 or more amino acids have been deleted from the carboxy-terminus.

Regarding the amendment to step iv) to recite "detecting the level of Drosophila RDGC GPCR phosphatase activity in the first and second samples from (iv); thereby detecting modulators of RDGC GPCR phosphatase activity," the specification does not provide support for this recitation. The specification provides support only for screening methods in which the results obtained with a test sample are compared to those obtained with a control sample that does not receive the test compound (see, e.g., page 22). The specification does not provide support for the concept of detecting the level of phosphatase activity in the first sample alone, or by comparing the first sample to an unspecified sample to thereby detect a modulator of RDGC phosphatase activity. To the extent that the change in level of phosphatase activity is detected by a comparison of the first and second sample, the specification also does not provide support for this concept. It is acknowledged that the specification provides basis for the concept of screening for modulators of RDGC GPCR phosphatase activity in which a mutant

rhodopsin is used as a substrate for RDGC phosphatase. However, the mutant rhodopsin lacking the C-terminal 18 amino acids is missing the residues which become phosphorylated and thereby the mutant rhodopsin is not hyperphosphorylated. The specification does not teach the concept that is encompassed by the present claims in which the results obtained in a second sample containing the truncated rhodopsin are compared to results obtained in a first sample containing rhodopsin to detect a change in level of Drosophila RDGC GPCR phosphatase, and to thereby identify a modulator of RDGC GPCR phosphatase activity.

Response to Remarks:

In the response, Applicants state that the specification teaches methods for screening for RDGC GPCR phosphatase modulators. Applicants point to page 22 of the specification as providing support for the concept that such methods can be performed *in vitro* or *in vivo*.

These arguments and the cited teachings in the specification have been fully considered but are not persuasive. The cited teachings provide support only for the general concept of a method of screening for RDGC GPCR phosphatase modulators *in vitro* or *in vivo*. The cited teachings do not provide support for the claimed concept of performing such methods by providing a second sample containing a mutant rhodopsin lacking the last 18 amino acids at the carboxy-terminus and a Drosophila RDGC phosphatase comprising SEQ ID NO: 1 and determining the level of RDGC GPCR phosphatase activity in the second sample in the presence and absence of a RDGC phosphatase mimetic.

The response states that the specification provides examples that include various conditions for comparison to normal RDGC phosphatase activity to determine its full extent of phosphatase activity on Rh1. It is stated that such comparisons include a comparison to a sample containing the mutant Rh1Δ356. Applicants acknowledge that Example 1 is not a method of screening for modulators of RDGC GPCR phosphatase activity. However, Applicants conclude that: "A skilled molecular biologist, familiar with the concept of controls, would understand that the mutant rhodopsin is used in Example 1 to ensure that the changes in phosphorylation of Rh1 (indicative of RDGC GPCR phosphatase activity) is entirely due to phosphorylation and dephosphorylation at the expected C terminal residues."

This argument has been fully considered but is not persuasive. Example 1 of the specification does not state that mutant rhodopsin is being used as a control. Rather, Example 1 indicates only that wildtype and rdgC mutant phosphoreceptor neurons were examined. Thereby, Applicant's statement does not accurately characterize the teachings in Example 1 of the specification. There are no teachings in the specification which indicate that the mutant Rh1Δ356 is analyzed in Example 1 so that a comparison can be made to wildtype RDGC to "ensure that the changes in phosphorylation of Rh1 (indicative of RDGC GPCR phosphatase activity) is entirely due to phosphorylation and dephosphorylation at the expected C terminal residues." Rather, the specification (page 44) teaches only that:

> Next, transgenic flies were generated that express a truncated rhodopsin molecule, RhlA356. This mutation eliminates the last 18 amino acid residues of rhodopsin, including the serines and threonines in the cytoplasmic tail. These residues are phosphorylated by GRKs. This truncated molecule was expressed

> in a ninaE mutant background such that the only rhodopsin present in photoreceptors was the one directed by the transgene. The truncated receptor was expressed in near normal amounts and the cells displayed normal light response. Rhodopsin was not hyperphosphorylated in Rh1A356 flies (Fig. 1B). In Figure I(B) the experiment in (A) was repeated with a 20 s pulse of light to quantitatively examine the rdgC phenotype. Upper panel; Autoradiogam of SDS-PAGE of 32po4 in vivo labeled retinal proteins. B denotes flies exposed to 20 s of blue light; BO denotes flies exposed to 20 s of blue light followed by 20 s of orange light. NinaE represents a null mutation in the structural gene for Rhl rdgC is a mutation in the RDGC phosphatase gene, and RhlA356 is the truncation of the last 18 residues of the COOH-terminal tail of rhodopsin. The results are representative of three independent experiments. Lower panel: The same gel blotted and probed with antibodies to Rhl. The truncation of rhodopsin results in a faster migrating polypeptide.

This is not equivalent to teaching the concept asserted by Applicants that mutant Rh1Δ356 is analyzed in Example 1 as a control for RDGC GPCR phosphatase activity.

The response states that the effect of the mutant RDGC "must be subtracted when considering the results for wild type rhodopsin, or one would not be 'detecting the level of Drosophila RDGC GPCR phosphatase activity.' The comparative value of the Rh1Δ356 sample is consistent with the concept of a control as it is understood in the art." This argument has also been fully considered but is not persuasive because the specification as originally filed does not teach that in Example 1, the effect of the mutant RDGC is subtracted from the results obtained with wildtype rhodopsin. Nor does the specification teach that in an assay to screen for modulators of RDGC GPCR phosphatase activity, the level of phosphatase activity obtained with the mutant Rh1Δ356 in the presence and absence of the test compound is subtracted from that obtained with the wildtype rhodopsin. Note also that Example 1 is characterized therein as disclosing a method wherein "RDGC was analyzed biochemically, physiologically,

and genetically to determine its activity as a GPCR phosphatase…First, the light dependent phosphorylation of rhodopsin in the wildtype and *rdgC* mutant photoreceptor neurons were examined" (page 43).

The response further states that the person of skill would recognize that the controls described in Example 1 "could be applied" to a method of screening. However, as noted by Applicants, Example 1 is not a screening method and does not include a step of contacting the claimed first and second samples with a test compound and determining RDGC GPCR phosphatase activity in first and second samples to determine if a test compound is a modulator of RDGC GPCR phosphatase activity. Thereby, the teachings in Example 1 cannot be relied upon to establish possession of the concept of using a control in a method of testing for modulators of RDGC GPCR phosphatase activity, wherein the control is a mutant rhodopsin lacking the carboxy-terminal 18 amino acids.

Applicants conclude that because control samples are known in the art, one would understand that a control would be used in a screening method, and that such a control sample with Rh1Δ356 would be an appropriate comparison in assays for RDGC GPCR phosphatase activity. This argument has also been fully considered but is not persuasive because the rejection under 35 USC 112 first paragraph (new matter) is not based on the obviousness of including a control, such as the Rh1Δ356 mutant, in a screening method, but is based on the finding that the originally filed specification did not provide basis for such a concept. The fact that controls were known in the art at the time the invention was made does not overcome the issue that the specification as

originally filed does not provide support for the limitation of using Rh1Δ356 as a control in an assay to screen for modulators of RDGC GPCR phosphatase activity. Obviousness is not the standard for the addition of new limitations to the disclosure as filed. Entitlement to a filing date does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed. Lockwood v. American Airlines Inc., 41 USPQ2d 1961 (Fed. Cir. 1977).

The response also states that the specification at pages 22 and page 9 provide examples of controls in screening assays. However, page 22 (beginning at line 27) teaches:

> "Modulation is tested using one of the in vitro or in vitro assays described herein. Samples or non-human animals that are treated with a potential RDGC phosphatase inhibitor or activator are compared to control samples or animals without the test compound, to examine the extent of modulation. Control samples or animals (untreated with activators or inhibitors) are assigned a relative RDGC phosphatase activity value of 100. Inhibition of RDGC is achieved when the RDGC phosphatase activity value relative to the control is about 90%, preferably 50%, more preferably 25%."

Accordingly, the specification at page 22 teaches only the concept of using a control sample or control animal that does not include the test compound. This is clearly distinct from the concept encompassed by the present claims wherein a rhodopsin mutant lacking the terminal 18 amino acids is used as the control.

At page 9, lines 18-21, the specification teaches:

> "RDGC mimetics are tested using assays for RDGC activity, e.g., rhodopsin mobility assays, and rhodopsin phosphorylation, as described below. When testing for an RDGC mimetic, wild-type RDGC is typically used as a positive control for RDGC activity. A relative activity value is assigned to RDGC, e.g., 100. Mimetic activity is achieved when mimetic RDGC activity relative to the control is about 25, more preferably 50-100."

Thereby, the specification teaches the concept that in assaying for RDGC mimetics for RDGC activity, the activity is compared to that of wildtype RDGC. The use of wildtype RDGC as a control is clearly distinct from the concept encompassed by the present claims wherein a rhodopsin mutant lacking the terminal 18 amino acids is used as the control in an assay to screen for modulators of RDGC GPCR phosphatase activity.

Lastly, the response states that the claims have been amended to recite that the mutant rhodopsin comprises wildtype rhodopsin lacking the last 18 amino acids at the carboxy terminus. It is stated that in view of the comprising language, the mutant must be as long as the wildtype lacking the 18 amino acids, but cannot be shorter.

These arguments and amendments to the claims have also been fully considered but are not persuasive. It is maintained that the specification teaches only one drosophila rhodopsin mutant in which the terminal 18 amino acids have been deleted – i.e., Rh1Δ356, - but does not teach any mutant rhodopsin that lacks the carboxy-terminal 18 amino acids. Further, since wildtype rhodopsin does not lack the carboxy-terminal 18 amino acids, it is unclear as to what would constitute a wildtype rhodopsin lacking the carboxy-terminal 18 amino acids. The specification as originally filed does not provide support for such a wildtype rhodopsin lacking the carboxy-terminal 18 amino acids. Also, since the claims do not define the “wild type” and do not define the length of the mutant rhodopsin, the use of the term “comprising” does not limit the length of the rhodopsin. Therefore, the claims still encompass mutants in which more than 18 amino acids are deleted from the COOH-terminus, such as mutants in which 19 or 20 or 21,

etc amino acids are deleted from the carboxy terminus as compared to Rh1. Accordingly, it is maintained that the specification provides basis only for a single rhodopsin mutant – i.e., mutant Rh1Δ356, in which only the COOH-terminal 18 amino acids have been deleted, but does provide support for any mutant rhodopsin in which 18 or more amino acids have been deleted from the carboxy-terminus.

Claim Rejections - 35 USC § 112, second paragraph

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 5-13, 15, 17, 19, 20 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 1, 5-13, 15, 17, 19, 20 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are the steps which establish a nexus between the step of providing a second sample comprising a mutant rhodopsin and Drosophila RDGC phosphatase and determining the RDGC GPCR phosphatase activity in the second sample that is contacted or not contacted with the test compound. The claims do not recite any method steps in which the second sample is utilized in the screening assay for modulators of RDGC phosphatase activity. Nor do the claims recite any type of relationship between the first and second samples. While the claims recite steps of determining the level of phosphatase activity in the first and second samples that are not contacted with a test

compound (i.e., steps (i) and (ii), and recite the step of determining the level of phosphatase activity in the first and second sample contacted with a test compound (step (iv)), the claims omit the essential steps that are required to determine if a test compound is a modulator of RDGC GPCR phosphatase activity. Determining the level of RDGC GPCR phosphatase activity in a sample is not equivalent to determining if a test compound is a modulator of RDGC GPCR phosphatase activity. Accordingly, the claims omit essential steps and elements that are required to accomplish the objective of detecting modulators of RDGC GPCR phosphatase activity..

Response to Remarks:

In the response, Applicants traversed the previous grounds of rejection. Applicants state that the claims have been amended to make clear that the second sample is utilized in the claimed method. However, this amendment does not clarify how detecting the level of RDGC GPCR phosphatase activity in the first and second samples, in the presence or absence of a test compound, thereby results in "detecting modulators of RDGC GPCR phosphatase activity." The claims do not set forth how detecting the level of phosphatase activity results in the detection of a modulator of phosphatase activity.

New Grounds of Rejection:

B. Claims 1, 5-13, 15, 17, 18, 20 and 22 are indefinite over the recitation of "mutant rhodopsin comprising wild type rhodopsin lacking the last 18 amino acids at the carboxy-terminus." This phrase is not defined in the specification and there is no art recognized definition for this phrase. The claims and specification do not define what is

intended to be encompassed by "wild type rhodopsin." However, the wildtype rhodopsin exemplified in the specification includes the carboxy-terminal 18 amino acids. Thereby, it is unclear as to what is meant by a wildtype rhodopsin lacking the last 18 amino acids at the carboxy-terminus. That is, if the carboxy-terminal 18 amino acids are missing, such a rhodopsin would not be considered to be a wildtype rhodopsin.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571)-272-0735.

The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

/Carla Myers/
Primary Examiner, Art Unit 1634